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#### REMARKS

Claims 1, 2, 6, 8, 9, 29, and 30 are pending and under consideration in the subject application.

#### Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 6, 8, 9, 29, and 30 are rejected under 35 U.S.C. §103(a) as obvious over Cancroft et al. (*Radiology* 106: 441-444, 1973), as evidenced by Socolow et al. (*Endocrinology* 80: 337-344, 1967), in view of Eskin et al. (*Obstetrics and Gynecology* 44: 398-402, 1974), Spitzweg et al. (*Journal of Clinical Endocrinology* 83: 1746-1751, 1998) and Jhiang et al. (*Endocrinology* 139: 4416-4419, 1998).

Applicants respectfully traverse this rejection for the following reasons. Applicants maintain that none of the references cited by the Examiner teach or suggest that the expression of mammary gland sodium/iodide symporter (mgNIS) in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in that subject. Applicants respectfully maintain that the Examiner's arguments that this feature of the present invention is obvious over the prior art is based on the principle of inherency.

Applicants note that "[i]nherency and obviousness are distinct concepts. *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966)." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555, 220 USPQ 303, 314 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Furthermore, "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). Finally, "[s]uch a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. See *In re Newell*, 891 F.2d 899, 901, 13 USPQ2d

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1248, 1250 (Fed. Cir. 1989).” In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

Applicants note the following statements by the Examiner as evidence that the Examiner’s position relies on a retrospective view of inherency that is not permitted under the law in a rejection based on obviousness. The Examiner stated that Cancroft et al. teach a method for diagnosing breast cancer in a subject, said method comprising scintigraphic imaging of tumor masses by administering  $^{99m}\text{Tc}$ -pertechnetate to the subject. The Examiner further stated that while Cancroft et al. teach that the mechanism of  $^{99m}\text{Tc}$ -pertechnetate concentration in malignant breast masses is not clear, it is an inherent feature of  $^{99m}\text{Tc}$ -pertechnetate to concentrate in the malignant breast masses by a mechanism involving its selective uptake by NIS, as evidenced by Socolow et al. and Spitzweg et al. [Emphasis added.] The Examiner then went on to express the opinion that “In the method of Cancroft, et al, the level of  $^{99m}\text{Tc}$ -pertechnetate taken up by a cancer cells reflects the level of expression in the cells of mgNIS, which is responsible for the uptake of  $^{99m}\text{Tc}$ -pertechnetate.” Applicants note that Cancroft et al. do not even mention the existence of “mgNIS” let alone that “the level of  $^{99m}\text{Tc}$ -pertechnetate taken up by a cancer cells reflects the level of expression in the cells of mgNIS.” Finally, in concluding the discussion regarding Cancroft et al., the Examiner stated that the diagnostic method of Cancroft et al. intrinsically detects the expression of mgNIS in the cancer cells. [Emphasis added.] Accordingly, Cancroft et al. do not teach that expression of mgNIS in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in the subject.

In discussing Socolow et al., the Examiner stated that Socolow et al. provide evidence that  $^{99m}\text{Tc}$ -pertechnetate is selectively taken up by the thyroid gland by a mechanism that resembles the mechanism by which radioiodide is taken up by the cells.

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Accordingly, Socolow et al. do not teach that expression of mgNIS in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in the subject.

In discussing Eskin et al., the Examiner stated that Eskin et al. teach that "pilot studies show that  $^{131}\text{I}$  concentration in biopsied human breast tissues with carcinoma or dysplasia is higher than in histologically normal tissues from the same patient" and that Eskin et al. conclude that the use of the diagnostic technique has several advantages, because of the fact that breast cancer takes up a greater amount of radioiodide.

Accordingly, Eskin et al. do not teach that expression of mgNIS in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in the subject.

The Examiner acknowledged that Cancroft et al. do not expressly disclose that the expression of mgNIS can be measured using an antibody or a nucleic acid probe, and indicated that those techniques are taught by Spitzweg et al. and Jhiang et al. Before discussing those two references, applicants would like to reiterate that Cancroft et al. do not even mention the existence of mgNIS, let alone teach a method to measure mgNIS expression.

The Examiner stated that Spitzweg et al. teach (1) a method for detecting the expression of human NIS using a nucleic acid probe that specifically hybridizes to mRNA encoding human NIS, (2) that the ability of thyroid tissue to selectively concentrate radioiodide is dependent upon the activity of NIS, which is commonly expressed in breast tissue also, and (3) that "the nucleotide sequences of hNIS cDNA derived from parotid gland, mammary gland, and gastric mucosa revealed full identity with the recently published human thyroid-derived NIS cDNA sequence." The Examiner also noted that Spitzweg et al. conclude "our detection of significant quantities of hNIS [human sodium/iodide symporter] gene expression in thyroid gland, salivary glands, thymus, pituitary gland, pancreas, testis, mammary gland, and gastric mucosa, and lower degrees of NIS gene expression in prostate, ovary, adrenal gland, lung, heart, and

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nasopharyngeal mucosa suggests that iodide transport in some of these tissues may be a specific property conferred by the expression of NIS." Applicants note that Spitzweg et al. did not study subjects with cancer and that Spitzweg et al. do not teach that expression of mgNIS in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in the subject.

The Examiner stated that Jhiang et al. teach the immunohistochemical analysis of human sodium/iodide symporter (NIS) expression. Applicants note that Jhiang et al. did not study NIS expression in breast tissue. Accordingly, Jhiang et al. do not teach that expression of mgNIS in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in the subject.

In summarizing the references, the Examiner stated in part that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to identify the presence of breast tissue that expresses relatively higher levels of mgNIS by either the method of Jhiang, et al or Spitzweg, et al, because Cancroft, et al teaches that a method that detects the differential concentration of  $^{99m}\text{Tc}$ -pertechnetate in breast cancer cells is diagnostic of breast cancer and because Eskin, et al teaches that breast cancer cells concentrate higher amounts of radioiodide than histologically normal breast tissue." Applicants maintain that since neither Cancroft et al. nor Eskin et al. teach that expression of mgNIS in the breast tissue of a nonlactating subject is indicative of the presence of breast cancer in the subject, there would have been no motivation to use the nucleic acid probe technique of Spitzweg et al. or the immunohistochemical technique of Jhiang et al. to look for the presence of mgNIS in the breast tissue of a nonlactating subject as an indication of the presence or absence of breast cancer in the subject.

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Applicants maintains that obviousness cannot be predicated on what was unknown prior to applicants' invention.

In summary, the references cited by the Examiner neither teach nor suggest each and every element of the claimed invention and do not render obvious the subject matter as a whole for which patent protection is sought. Accordingly, reconsideration and withdrawal of the ground of rejection under 35 U.S.C. §103(a) is respectfully requested.

#### Information Disclosure Statement

The Office Action Summary sheet indicates that a copy of applicants' previously submitted PTO-1449 (substitute) was attached to the April 8, 2003 Office Action. However, no such forms were received with the Office Action. Applicants request that the Examiner attach a copy of the forms to the next communication from the Patent Office.

#### Conclusion

In light of the above remarks, applicants respectfully request withdrawal of the rejection set forth in the April 8, 2003 Office Action and passage of currently pending claims 1, 2, 6, 8, 9, 29, and 30 to allowance. If there are any minor matters that would prevent allowance of the claims, applicants request that the Examiner contact the undersigned attorney.


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It is believed that no fee is required to maintain the pendency of the subject application. However, if there are any unanticipated fees required to maintain the pendency of this application, the PTO is authorized to withdraw those fees from Deposit Account 01-1785.

Respectfully submitted,

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